UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/765,727 | 01/23/2004 | Mark William Bodmer | 674525-2010 | 2653 |

20999 7590 10/16/2007

FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

| EXAMINER | |
|---|---|
| BUNNER, BRIDGET E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 10/16/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/765,727 | BODMER ET AL. | |
| | Examiner | Art Unit | |
| | Bridget E. Bunner | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *8,10,12,14,31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,11,13 and 15-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-32* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/23/04 and 9/28/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/04;2/10/04;4/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election of Group I, claims 1-32 in the reply filed on 07 August 2007 is acknowledged. Applicant's election of species (a) a protein or polypeptide comprising a Notch ligand DSL domain is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

As discussed in the restriction election of 07 March 2007, upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104.

Claims 8, 10, 12, 14, and 30-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07 August 2007.

Claims 1-7, 9, 11, 13, and 15-30 are under consideration in the instant application as they read upon the elected invention of contacting a cell with a modulator of Notch signaling wherein the modulator is an activator of Notch signaling.

### *Information Disclosure Statement*

It is noted the Hoyne reference listed on information disclosure statement filed 27 April 2004 has been crossed off by the Examiner. This reference has been considered and was listed on the information disclosure statement of 23 January 2004.

### *Priority*

Acknowledgment is made of applicant's claim for foreign priority based on applications filed in the United Kingdom on 7/25/01, 4/5/02/ and 5/28/02 (2). It is noted, however, that applicant has not filed a certified copy of UK 0118153.6, 0207930.9, 0212282.8, and 0212283.6 applications as required by 35 U.S.C. 119(b).

### *Specification*

1. The disclosure is objected to because of the following informalities:

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "CONTACTING CELLS WITH MODULATORS OF NOTCH SIGNALLING".

3. The Brief Description of the Drawings for Figures 4-30 at pages 12-13 of the specification is not descriptive. For example, the specification simply states "Figure 8 shows the results of Example 4". However, according to MPEP § 608.01(f) and CFR 1.74, when there are drawings, there shall be a brief description of the several views of the drawings and the detailed description of the invention shall refer to the different views by specifying the numbers of the figures, and to the different parts by use of reference letters or numerals.

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 31, line 19). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

***Claim Objections***

5. Claims 2-7, 9, 11, 13, 17-22, 24, and 27-30 are objected to because of the following informalities:

6. Claims 2-7, 9, 11, 13, 17-22, 24, and 27-30 use the acronyms "TNF", "TNFα", "IL-5", "IL-13", "IL-10", "IL-2", "IFNγ", "TH2", "TH1", "DSL" and "EGF" without first defining what they represents in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-7, 9, 11, 13, and 15-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 1-7, 9, 11, 13, and 15-30 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating that cytokine expression is modified in a cell.

9. The term "an immune modulatory cytokine profile" in claims 17-20 is a relative term which renders the claim indefinite. The term "an immune modulatory cytokine profile" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear if this is referring to gene or protein expression in a specific disease state. It is also not clear what cytokines the profile encompasses.

10. Claim 30 is indefinite because the elements recited in the claim do not constitute proper Markush groups. The claim is indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

11. The term "EGF-like" in claim 29 is a relative term which renders the claim indefinite. The term "EGF-like" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what regions, domains, variants, etc. this term is encompassing.

12. Claim 30 recites the limitation "EGF domain" in line 1. There is insufficient antecedent basis for this limitation in the claim. It is noted that claim 30 depends from claim 29 which recites "EGF-like domain".

13. Claim 22 is rejected as being indefinite because it is not clear what patient population or conditions require the reduction of a TH1 immune response.

14. Claim 27 is rejected as being indefinite because it is not clear what diseases are associated with excessive TNFα, excessive IL-5 production, or excessive IL-13 production.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 21-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims recite methods for reducing a TH2 and TH1 immune response in a subject in need thereof comprising administering a cell in which cytokine expression is modified or a modulator of Notch signaling, to the subject. The claims recite a method for treating inflammation, an inflammatory condition or an autoimmune condition comprising administering a cell in which cytokine expression is modified or a modulator of Notch signaling, to the subject. Finally, the claims recite a method for treating a disease associated with excessive TNFα production, excessive IL-5 production or excessive IL-13 production, comprising administering a cell in which cytokine expression is modified or a modulator of Notch signaling, to the subject.

The specification teaches several assays wherein CD4+ T cells are stimulated with either soluble mouse Fc-delta1 or solid phase (plated) mouse Fc-delta1 and cytokine levels (IL-10, IL-13, IFNγ, IL-2) are measured (see Examples 5-7, pages 97-99; Figures 9-11). T cell assays are carried out with CD4+ T cells and Streptavidin-coated Dynabeads, supernatants are removed, and IL-10 and IL-13 are measured by ELISA (page 106, Example 10; Figure 13). Furthermore, the specification discloses that human CD4+ T cells are stimulated to produce cytokines with

anti-CD3/CD28 T cell expander beads, plate bound anti-CD3, or soluble anti-CD28 (page 106, lines 31-32; page 107, lines 1-2). Beads coated with mouse Delta1EC domain-hIgG4 fusion protein are also added to the cell wells (page 107, lines 2-6). Supernatants are removed and cytokine production is measured by ELISA (page 107, lines 6-12; Figures 14-19). Figures 14-19 indicate that mDelta1-Fc enhances IL-10 production and decreases IFNγ and IL-5 production.

The specification of the instant application also teaches that "the term 'modulator' may refer to antagonists or inhibitors of Notch signalling, i.e. compounds which block, at least to some extent, the normal biological activity of the Notch signalling pathway. Conveniently such compounds may be referred to herein as inhibitors or antagonists. Alternatively, the term "modulator" may refer to agonists of Notch signalling, i.e. compounds which stimulate or upregulate, at least to some extent, the normal biological activity of the Notch signalling pathway. Conveniently such compounds may be referred to as upregulators or agonists." (page 17, lines 22-28). The specification also teaches that candidate modulators may be organic small molecules, polypeptides, a nucleotide sequence, an antibody, synthetic compounds, or natural isolated compounds (bottom of page 17 through page 19). The specification discloses that agonistic modulators may include noggin, chordin, Follistatin, Xnr3, fibroblast growth factors, a Notch ligand (or polynucleotide encoding a Notch ligand), a constitutively active Notch receptor or Notch intracellular domain (or polynucleotide encoding such), among others (see page 24 through page 25).

However, the specification of the instant application does not teach administering any cell in which cytokine expression is modified or administering any modulator of Notch signaling to any subject. Undue experimentation would be required of the skilled artisan to determine the

optimal dosage, duration, and route of administration of all possible Notch modulators or Notch activators. The specification also does not disclose activating any other cells other than T cells.

In mammals, the Notch ligand proteins (Delta, Delta-like-1, -3, and -4, and Jagged-1 and -2) have extracellular domains containing multiple EGF-repeats as well as a characteristic cysteine-rich region referred to as the Delta-Serrate-Lag-2 (DSL) domain (McKenzie et al. Sem Cell Dev Biol 14: 127-134, 2003; page 128, column 1, 1st paragraph). The DSL domain and EGF repeats are conserved between all the Notch ligands, but the Jagged proteins contain a distinct cysteine-rich region immediately proximal to the transmembrane pass (McKenzie et al., page 128, column 1, 1st paragraph). McKenzie et al. state that since this feature is not present in the Deltas, this suggests distinct biological functions for the Jagged and Delta family (McKenzie et al., page 128, column 1, 1st paragraph). Importantly, McKenzie et al. point out that "in mammalian systems, little is known about the extent to which different Notch ligands activate different receptors under physiological conditions, and whether there are distinct downstream signaling events triggered by different ligand/receptor combinations" (page 128, column 1, 1st paragraph). Thus, one skilled in the art would not be able to predict that all possible modulators of Notch or all activators of Notch would reduce a TH1 immune response; reduce a TH2 immune response; treat inflammation, an inflammatory condition, or an autoimmune condition; or treat a disease associated with excessive TNFα production, excessive IL-5 production, or excessive IL-13 production, as required by the instant claims.

Additionally, it is noted that the various inflammatory conditions and autoimmune conditions encompassed by the instant claims and disclosed in the specification have different pathophysiologies. For example, rheumatoid arthritis is a chronic, systemic inflammatory

disease that is characterized by synovial inflammation and structural damage of articular cartilage and subchondral bone (pg 325-326; Elgert, K. Immunology, understanding the immune system. New York: Wiley-Liss, Inc., 1996). Graves' disease is a disorder of the thyroid gland that is caused by autoantibodies that stimulate thyroid cellular activity by displacing thyroid-stimulating hormone binding (Elgert, K., pg 324, col 2). Asthma is characterized by a constriction of the bronchioles of the lung wherein the tissue surrounding the capillaries of the lung contains mast cells, which, when stimulated by allergen, release histamine, causing contraction of the smooth muscles (Elgert, K., pg 305, col 2). Undue experimentation would be required of the skilled artisan to administer all possible Notch modulators or Notch activators to individuals with all possible inflammatory conditions or autoimmune conditions and treat the condition. One skilled in the art would also not be able to predict from the of the instant specification that Notch modulators or Notch activators would be able to treat all possible inflammatory or autoimmune conditions because inflammatory and autoimmune conditions have different pathophysiologies.

Due to the large quantity of experimentation necessary to administer all possible Notch modulators or Notch activators to reduce a TH2 immune response, reduce a TH1 immune response, treat an inflammatory or autoimmune condition, and treat a disease associated with excessive production of TNFα, IL-5, or IL-13; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; the unpredictability of the *in vivo* effects of Notch modulators or Notch activators on the reduction of a TH2 immune response, reduction a TH1 immune response, treatment an inflammatory or autoimmune condition, and treatment a disease

associated with excessive production of TNFα, IL-5, or IL-13; and the breath of the claims which fail to recite limitations for Notch modulators or Notch activators, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

16. Claims 1-7, 9, 11, 13, 15-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for modifying cytokine expression in a cell comprising contacting the cell with a modulator of Notch signaling. The claims also recite a method for generating, in a cell, an immune modulatory cytokine profile with (a) increased IL-10 expression and (b) (i) reduced TNFα expression, (ii) reduced IL-5 expression or (iii) reduced IL-13 expression comprising contacting the cell with a modulator of Notch signaling. The claims recite methods for reducing a TH2 and TH1 immune response in a subject in need thereof comprising administering a cell in which cytokine expression is modified or a modulator of Notch signaling, to the subject. The claims recite a method for treating inflammation, an inflammatory condition or an autoimmune condition comprising administering a cell in which cytokine expression is modified or a modulator of Notch signaling, to the subject. Finally, the claims recite a method for treating a disease associated with excessive TNFα production, excessive IL-5 production or excessive IL-13 production, comprising administering a cell in which cytokine expression is modified or a modulator of Notch signaling, to the subject.

The claims do not require that the modulator of Notch signaling or the activator of Notch signaling possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing features. Thus, the claims are drawn to a genus of modulators of Notch signaling and activators of Notch signaling.

The specification of the instant application teaches that "the term 'modulator' may refer to antagonists or inhibitors of Notch signalling, i.e. compounds which block, at least to some extent, the normal biological activity of the Notch signalling pathway. Conveniently such compounds may be referred to herein as inhibitors or antagonists. Alternatively, the term "modulator" may refer to agonists of Notch signalling, i.e. compounds which stimulate or upregulate, at least to some extent, the normal biological activity of the Notch signalling pathway. Conveniently such compounds may be referred to as upregulators or agonists." (page 17, lines 22-28). The specification also teaches that candidate modulators may be organic small molecules, polypeptides, a nucleotide sequence, an antibody, synthetic compounds, or natural isolated compounds (bottom of page 17 through page 19). The specification discloses that agonistic modulators may include noggin, chordin, Follistatin, Xnr3, fibroblast growth factors, a Notch ligand (or polynucleotide encoding a Notch ligand), a constitutively active Notch receptor or Notch intracellular domain (or polynucleotide encoding such), among others (see page 24 through page 25).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making

the claimed product, or any combination thereof. In this case, there is not even identification of any particular structure or function that must be conserved. The specification of the instant application does not teach any specific modulators of Notch signaling or activators of Notch signaling. The brief description in the specification is not adequate written description of an entire genus of Notch modulators and activators encompassed by the claimed methods.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the Notch modulators and Notch activators of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The Notch signaling, immune signaling, second signal, and third signal are required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

Therefore, only a specific Notch modulator and Notch activator, but not the full breadth

of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1, 15, 16-20, and 28-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6-8, 11-16 of copending Application No. 11/178,724. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to contacting a cell with a modulator of Notch signalling. The preamble of claim 1 of the instant application broadly recites "a method for modifying cytokine expression in a cell" while the preamble of claim 1 of the '724 application recites "a method for modifying IL-4 expression". Furthermore, although

the preambles of the remaining independent claims in both cases are slightly different, the process step in the body of the claims is the same (i.e., "contacting a cell with a modulator of Notch signaling") and does not depend on the preamble for completeness.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 22-23, 27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 11/071,796. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to administering a modulator of Notch signaling. Claims 21-23 of the instant application broadly recite methods for reducing a TH1 immune response and for treating inflammation, an inflammatory condition or an autoimmune condition while claim 1 of the '796 application recites a method of treating Graft Versus Host Disease. It was well known at the time the invention was made that TH1 cells and cytokines, such as TNFα, IFNγ, and IL-2, promote Graft Versus Host Disease (see for example Fowler et al. Leukemia Lymphoma 38(3-4): 221-234, 2000; Figure 1, page 223;; Jacobson, DA Expert Opin Invest Drugs 11(9) : 1271-1280, 2002 ; page 1272, bottom of column 1 through column 2).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-7, 9, 11, 13, 15, 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/03743 (Gehring et al., 18 January 2001).

Gehring et al. teach methods for altering the fate of a cell, tissue, or organ type by altering Notch pathway function in the cell (page 19, lines 29-30). Specifically, Gehring et al. disclose contacting a cell with an agonist of Notch and an agonist or antagonist of a cell fate control gene pathway (page 20, lines 9-13, 32-35). Gehring et al. teach that cells in which cell fate may be altered include, for example, fibroblasts and epithelial cells (page 52; page 55, lines 1-13; page 58, lines 14-24; page 60, lines 6-11).

It is noted that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Furthermore, since Gehring et al. teach contacting a cell with an agonist of Notch, the modification of cytokine expression and the generation of an immune modulatory cytokine profile must have been inherently occurring in the prior art of Gehring et al., absent evidence to the contrary (see *Ex parte Novitski*, 26 USPQ2d 1389 (BPAI 1993) ; see also *Integra LifeSciences I Ltd. V. Merck KGaA*, (DC SCalif) 50 USPQ2d 1846). Inherent anticipation does not require that one of ordinary skill in the art recognize an inherent feature in a prior art disclosure (*Schering Corp. v. Geneva Pharmaceuticals Inc.*, 67 USPQ2d 1664 (CAFC 2003); *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)).

19. Claims 1-7, 9, 11, 13, 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,780,300 (Artavanis-Tsakonas et al.).

Artavanis-Tsakonas et al. teach methods for the expansion of non-terminally differentiated cells by activating the Notch pathway in precursor cells (column 8, lines 59-63). Artavanis-Tsakonas et al. also teach that activation of the Notch pathway is achieved by contacting the cell with a Notch ligand (column 9, lines 5-11). Artavanis-Tsakonas et al. disclose that the Notch pathway is a signal transducing pathway comprising elements which interact, genetically and/or molecularly, with the Notch receptor protein (column 12, lines 30-38).

As discussed above, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Furthermore, since Gehring et al. teach contacting a cell with an agonist of Notch, the modification of cytokine expression and the generation of an immune modulatory cytokine profile must have been inherently occurring in the prior art of Gehring et al., absent evidence to the contrary (see *Ex parte Novitski*, 26 USPQ2d 1389 (BPAI 1993) ; see also *Integra LifeSciences I Ltd. V. Merck KGaA*, (DC SCalif) 50 USPQ2d 1846). Inherent anticipation does not require that one of ordinary skill in the art recognize an inherent feature in a prior art disclosure (*Schering Corp. v. Geneva Pharmaceuticals Inc.*, 67 USPQ2d 1664 (CAFC 2003); *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)).

***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
12 October 2007

Bridget E. Bunner

BRIDGET E. BUNNER
PRIMARY EXAMINER